Knowing me, knowing you

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Introduction

Dealing with society

Managing yourself in the social environment is by no means an easy task. It includes several complex social cognitive and emotional processes that most of us take for granted. Brothers [(1990); page 27] defined social cognition as "*the processing of any information which culminates in the accurate perception of the dispositions and intentions of other individuals*". Such complex social cognitive processes encompass, amongst others, the ability to interact in the social world by interpreting social and emotional cues sent out by others and using them in understanding other peoples' intentions and beliefs; this ability is referred to as Theory of Mind (ToM). Besides understanding others people's intentions, emotional processing is important in this "social environment management" and for personal well-being. This includes the interpretation of emotional events and dealing with the subsequent evoked emotional response as well as using the knowledge from previous social encouters in new situations. Evaluating one's own behavior and characteristics in light of these situations is crucial for adequate adaptation to a social environment.

Sometimes these social cognitive and emotional processes are hampered, for example in patients with psychiatric disorders, such as schizophrenia, bipolar disorder and autism (Baron-Cohen et al., 1985; Corcoran et al., 1995; Langdon et al., 2002; Leslie & Thaiss, 1992; Pinkham et al., 2003). This thesis focussed on the underlying neural mechanisms of social cognitive and emotional impairments in patients with psychiatric disorders, relatives of these patients and individuals who are vulnerable for development of a psychiatric disorder. Moreover, the mediating effect of impaired social cognitive and emotional processes on patient's understanding of their illness and their acceptance of treatment – also referred to as illness ***insight*** – was discussed.

Psychiatric disorders: schizophrenia and bipolar disorder

The aim of this thesis was to shed more light upon and provide tools towards insight in patients with schizophrenia and bipolar disorder. In 1854 two French scientists independently described a similar phenomenon distinguishing between a state of elevated mood and melancholia. Falret (1851) launched the term "folie circulaire" or circular insanity. Three years later Baillarger (1854) came up with the term "folie à double forme" referring to two phases of insanity, one of depression and one of excitation. The main difference between both definitions was that Falret (1851) included a period of intermission with full recovery, while in Baillarger's (1854) definition these intermission periods were not symptom free.

This work led Kraepelin (1896; 1919) to differentiate dementia preacox and manic depressive insanity. He defined the concept of dementia praecox as a chronic progressively deteriorating disorder, emphasizing the cognitive deterioration (dementia) and the early onset (praecox), while he unified mania, depression and bipolar disorder under one denominator, manic-depressive insanity (Angst, 2002).

The difference lay mainly in the prognosis of the disorder, which was worse for dementia praecox. The term schizophrenia was first introduced by Bleuler (1911) who refined the description of dementia praecox. Bleuler introduced the 'group of schizophrenia's' and by that the notion that the disorder is hard to define and may present itself in several subtypes that vary in severity. Most importantly, Bleuler distinghuised four symptoms also called the four A's: autism, ambivalence, associative loosening, and affective disturbances. These symptoms alone were necessary for a diagnosis of schizophrenia were not present in more latent and simple subtypes of schizophrenia and were therefore considered less important (Bleuler, 1911).

Similarly, clinical manifestations for bipolar disorder are very heterogeneous, ranging from mild forms of depression and/or hypomania to more severe manifestations of both symptoms including in some cases the occurrence of a psychotic episode (Muller-Oerlinghausen et al., 2002). At present, the Diagnostic and Statistical Manual, fourth edition [DSM-IV; (1994)] and the International Classification of Diseases, tenth edition [ICD-10; (1994)] are widely used as classification systems, which include specified diagnostic criteria for schizophrenia as well as for mood disorders, such as bipolar disorder. Even though these tools do not take away the complexity of both disorders, the use of systematic interviews based on the DSM or ICD criteria ensures that similar diagnostic criteria for both disorders are used worldwide, which increases the reliability of the diagnosis.

Schizophrenia is a severe and chronic psychiatric condition characterized by a wide range of symptoms that can be categorized into positive and negative symptoms (Mueser & McGurk, 2004). Positive symptoms refer to phenomena that should not be present, such as delusions, hallucinations, incoherence and grossly disorganized or catatonic behavior. Negative symptoms on the other hand include behavior or experiences that lack in schizophrenia patients and are referred to as flattened affect, social withdrawal, apathy and poverty of speech. Besides positive and negative symptoms, cognitive symptoms (memory, executive function and attention impairments) and affective dysregulation can be distinguished (van Os & Kapur, 2009). Finally, schizophrenia is often accompanied by prominent dysfunctions in the social and occupational domain.

Approximately one percent of the population is affected by schizophrenia during their lifetime (Evers & Ament, 1995). The time of onset of schizophrenia typically occurs during adolescence or in young adulthood. The chronicity of the disorder is illustrated by a study investigating the course of schizophrenia in first episode patients (Wiersma et al., 1998). Only 12 % of the patients recovered after the first psychosis and only 15 % of the patients after two or more psychotic episodes (Wiersma et al., 1998). Of the other patients, about 17 % of the patients partially recovered after their first episode and in about 33 % of the patients a negative syndrome (the umbrella term for all negative symtoms) remained. The illness was chronic in 11% of the patients. Thus, while not all patients with a first episode

psychosis become chronically ill, in the majority of the patients (61%) at least some symptoms remain.

Bipolar disorder is characterized by the occurance of one or more manic, hypomanic or mixed episodes. A manic episode is characterized by a state of euphoria, irritability or disinhibition. Furthermore, in almost all cases also more or less severe depressive episodes occur in which the patient is in a state of sadness, lowered mood, loss of interest and loss of pleasure in previously enjoyed activities (anhedonia). The DSM-IV makes a distinction between bipolar I and bipolar II disorder. In bipolar I disorder manic episodes occur and may be alternated with depressive episodes, while in bipolar II disorder, depressive episodes are alternated with hypomanic (never manic) episodes. Furthermore, the DSM-IV distinguishes cyclothymic disorder, which refers to the rapid occurrence of numerous (hypo) manic episodes as well as numerous depressive symptoms within in a two-year time span. Besides mood symptoms, psychotic features can occur during manic or depressive episodes in patients with bipolar disorder. Especially in these cases a differential diagnosis distinguishing between schizophrenia or bipolar disorders can be difficult. Just like in schizophrenia, the first episode usually occurs in early adulthood (Nolen & Koerselman, 2000).

The lifetime prevalence of bipolar disorder is somewhat higher than for schizophrenia, approximately 1.5% - 2% (Kupka & Regeer, 2007; Muller-Oerlinghausen et al., 2002), and the prevalence among men and women is approximately similar, between 1,6% - 2,2% respectively (Bijl et al., 1997; Kupka & Regeer, 2007). About 80% of the bipolar patients have recurrent episodes (Kupka & Nolen, 1999). Suicide rate in bipolar disorder is approximately two or three times higher than in the general population (Muller-Oerlinghausen et al., 2002).

In both schizophrenia and bipolar disorder, cognitive and emotional impairments have been described (Aleman et al., 1999; Phillips et al., 2003; Van der Werf, 2010). In this thesis, we focussed on the social cognitive and emotional impairments in both disorders. More specifically, the ability to take the perspective of someone else, the regulation of emotional experiences and the evaluation of one's traits and characteristics were discussed. Furthermore, the illness insight of the patient was discussed for both disorders. More specifically, the importance of the aforementioned social cognitive and emotional impairments for illness insight (specifically with regard to psychosis) were highlighted. Finally, directions for future research were given and possible implications for clinical purposes were discussed.

Neurobiology

Since the use of techniques like structural and functional Magnetic Resonance Imaging for investigating brain functioning in psychiatric patients, a large number of research papers has been published that reported structural and functional abnormalities in both disorders.

Schizophrenia. Structural abnormalities have been reported for patients with schizophrenia in the dorsolateral prefrontal cortex (Glantz & Lewis, 2000), superior temporal and parietal regions (Plaze et al., 2009). Cortical thinning was found in frontal, superior temporal and temporo-parietal regions (Ettinger et al., 2010; Rimol et al., 2010; Yang et al., 2010). Wright et al. (2000) reported overall smaller cerebral volume in patients with schizophrenia, while vetricular volume was larger. They also reported reduced bilateral amygdala volume, which is important for emotional processing. Furthermore, studies investigating white matter in schizophrenia reported reduction in patients compared to healthy controls [see Konrad et al. (2008) for an overview]. Such white matter reductions in the frontal cortex have been associated with functional impairments (Ho et al., 2003). These cortical and white matter reductions have already been demonstrated in first-episode patients, suggesting that it is not a result of the chronicity of the disorder (Paillere-Martinot et al., 2001).

Besides structural abnormalities, functional abnormalites have been reported. In a recent review on the neuroanatomy of symptom dimensions, Goghari et al. (2010) concluded that negative sympomts were predominantly related to abnormal functioning of the ventrolateral prefrontal cortex and the ventral striatum, while positive symptoms were related to abnormal functioning of the amygdala, medial frontal and (para)hippocampal regions. In addition, Goghari et al. (2010) showed that impaired functioning of the dorsolateral prefrontal cortex was related to disorganised symptoms. Furthermore, a large body of evidence has demonstrated decreased prefrontal activation in patients with schizophrenia in response to cognitive tasks [see Tan et al. (2007) for an overview]. Such functional abnormalities in prefrontal activation was also shown in medication naïve and first episode patients, which tells us that these abnormalities are not due to medication or duration of illness (Barch et al., 2001). Jardri et al. (2010) demonstrated in a recent meta-analysis that increased activation in fronto-temporal and parietal regions is related to the experience of auditory verbal hallucinations. Thus, while impaired cognitive functioning seems to be related to a decrease in prefrontal regions, the presence of auditory verbal hallucinations has been associated with increased activation in prefrontal as well as temporal and parietal areas. Furthermore, abnormal functional connectivity was demonstrated during resting state in fronto-temporal networks for schizophrenia (Broyd et al., 2009). This abnormal connectivity has been related to the presence of auditory verbal hallucinations (Vercammen et al., 2010a; Wylie & Tregellas, 2010). In addition, such deviant fronto-temporal connections have been associated with cognitive dysfunction (Ragland et al., 2007; Townsend et al., 2010).

Not only impaired cognitive, but also impaired emotional functioning has been associated with abnormal activation patterns in patients with schizophrenia. Aleman and Kahn (2005) reviewed the available evidence on the neural correlates of emotional dysfunction and proposed that the volume reduction of the amygdala in combination with the decreased anatomical connectivity between the amygdala and

the frontal cortex results in abberant emotion recognition and expression. Similarly, abnormal activation patterns in the ventral striatum have been demonstrated for reward processing in patients with schizophrenia, which may be important for affective learning (Ochsner, 2008). Furthermore, abnormal activation patterns in the insula in schizophrenia patients have been associated with an abberant sense of self (Wylie & Tregellas, 2010).

Bipolar disorder. Structurally, cortical thinning in frontal, superior temporal and temporo-parietal regions bipolar I disorder was reported (Rimol et al., 2010). A recent meta-analysis reported reductions in the bilateral insula and anterior cingulate cortex (Ellison-Wright & Bullmore, 2010), while another recent meta-analysis demonstrated decreased overal brain volume and increased ventricular and globus pallidus volume, but no differences for amygdala or insular volume (Arnone et al., 2009). In a large study with 321 bipolar I patients, Hallahan et al. (2010) reported increased right lateral ventrical volume as well as increased volume in the left temporal cortex and right putamen. Of note, they found a positive interaction between the size of the amygdala and hippocampus and the use of lithium. Relationships between the number of affective episodes and abnormalities in prefrontal areas, striatum and amygdala have also been reported (Strakowski et al., 2005).

With regard to functional neuroimaging findings, evidence suggests dysfunctioning of the striatal-thalamic-prefrontal cortex network as well as the amygdala and midline cerebellum that may result in impaired regulation of mood (Strakowski et al., 2005). Green et al. (2007) showed increased limbic activation upon emotional stimuli as well as a relationship between impaired executive functioning and prefrontal cortex activation in bipolar disorder. Like in schizophrenia, cognitive dysfunctioning in bipolar disorder is mostly related to hypoactivation in the dorsolateral prefrontal regions (Altshuler et al., 2005; Glahn et al., 2005; Lesh et al., 2010; Ragland et al., 2007; Townsend et al., 2010). Altshuler et al. (2008) demonstrated that decreased activation in the orbitofrontal cortex was similar in depressive and manic states of bipolar disorder, while left dorsolateral prefrontal activation was decreased in a manic state, but increased in a depressed state of the disorder. Not only in patients, but also in first degree relatives of patients with a psychotic disorder similar, but less severe, neurocognitive abnormalities have been reported (Fusar-Poli et al., 2007). In addition, abnormal functional connectivity has been demonstrated during resting state in fronto-temporal networks for bipolar disorder (Dickstein et al., 2010). Such deviant fronto-temporal connections have been associated with cognitive dysfunction (Ragland et al., 2007; Townsend et al., 2010).

In sum, structural and functional abnormalities have been widely reported for both bipolar disorder as well as for schizophrenia. Mostly, these abnormalities point towards frontal, temporal and limbic regions, areas that have been implicated in, amongst others, social cognitive and emotional processing (see figure 1 for a graphical representation of these regions). Both similarities and differences between bipolar disorder and schizophrenia in structural and functional imaging data have

been reported. In general, volume reductions seem to be larger in patients with schizophrenia (Arnone et al., 2009; Ellison-Wright & Bullmore, 2010). Similarly, the degree of hypoactivation in dorsolateral prefrontal areas during cognitive tasks seems to be greater in schizophrenia than in bipolar patients (Hamilton et al., 2009). Furthermore, while for schizophrenia patients most structural and functioning evidence points towards a wider network of abnormalities in patients with schizophrenia encompassing frontal, limbic and temporo-parietal regions, for bipolar disorder most abnormalities have been reported in limbic and prefrontal areas.

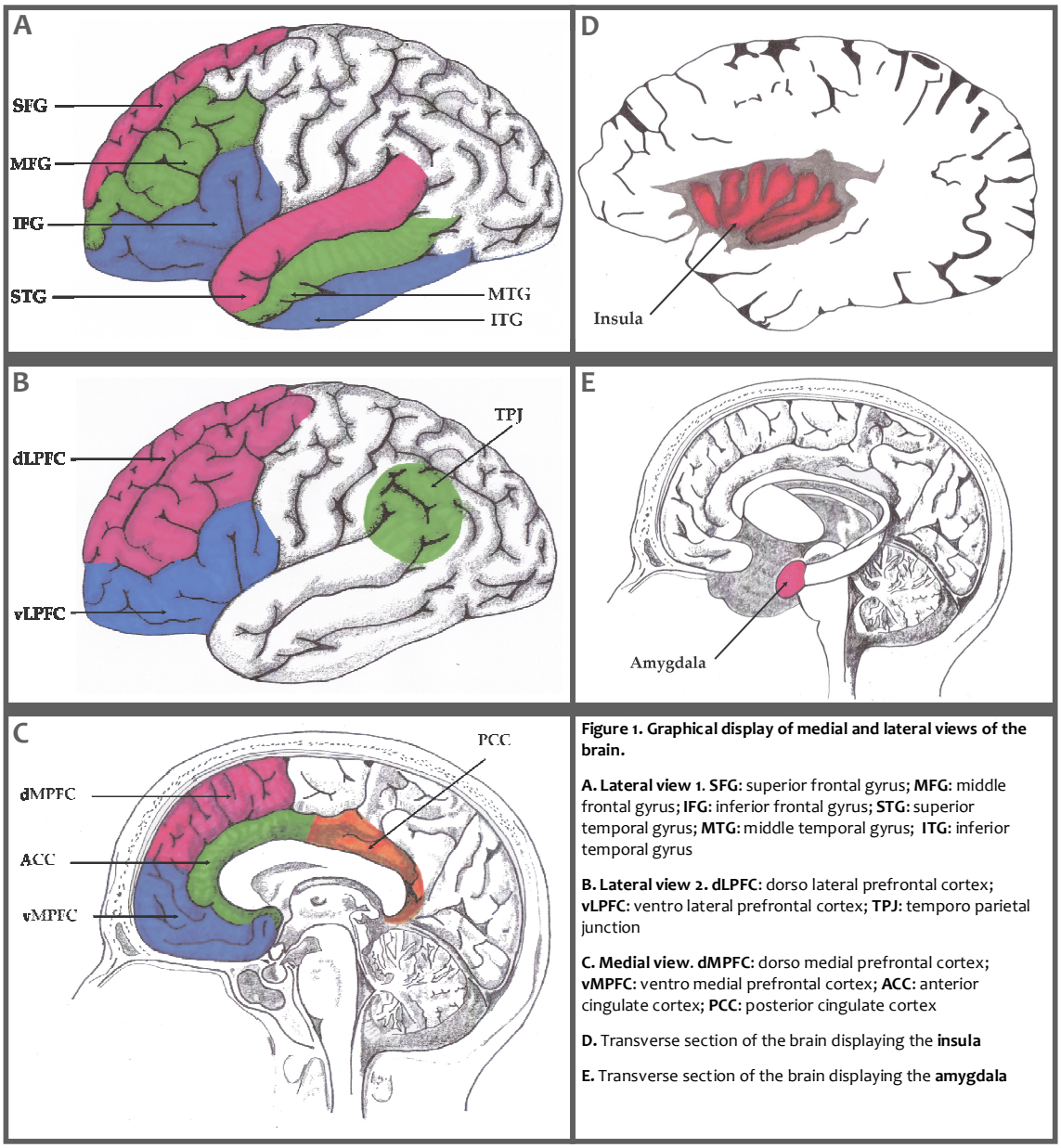

Figure 1. Graphical display of medial and lateral views of the brain.

A. Lateral view 1. SFG: superior frontal gyrus; **MFG:** middle frontal gyrus; **IFG:** inferior frontal gyrus; **STG:** superior temporal gyrus; **MTG:** middle temporal gyrus; **ITG:** inferior temporal gyrus

B. Lateral view 2. dLPFC: dorso lateral prefrontal cortex; **vLPFC:** ventro lateral prefrontal cortex; **TPJ:** temporo parietal junction

C. Medial view. dMPFC: dorso medial prefrontal cortex; **vMPFC:** ventro medial prefrontal cortex; **ACC:** anterior cingulate cortex; **PCC:** posterior cingulate cortex

D. Transverse section of the brain displaying the **insula**

E. Transverse section of the brain displaying the **amygdala**

Interacting with the social world

The ability to think about thoughts and beliefs of oneself and others in our social environment is crucial for interacting with other people (Premack & Woodruff, 1987). This capacity is also referred to as Theory of Mind (ToM). ToM is a broad concept encompassing the capacity to understand other people's mental state. This understanding can refer to how other people are feeling emotionally, but can also refer to the understanding that the other person may have a different belief or knowledge in a given situation as well as the understanding of the subsequent behavior of this other person [see Wellman et al. (2001) for a meta-analysis]. The past decade has shown a surge of interest in the neural basis of ToM [see Carrington & Bailey (2009) for a review]. Neuroimaging studies revealed involvement of several brain regions, such as the temporo-parietal junction (TPJ), the superior temporal sulcus (STS), anterior cingulate cortex (ACC) and orbital and medial frontal areas (Apperly et al., 2004; Carrington & Bailey, 2009; Decety & Jackson, 2004; Frith & Frith, 1999; Ruby & Decety, 2003; Saxe & Kanwisher, 2003). To date, the development of ToM as as well as how ToM is instantiated in the brain is an ongoing subject of research.

Describing ToM as just the ability to infer another persons perspective and understanding their intentions does not render justice to its complexity. Instead, ToM has been regarded as a complex social cognitive ability consisting of multiple processes. Taking another's perspective is often regarded as a core feature of ToM. However, it has been suggested that the inhibition of the own perspective may well be a necessary feature of perspective taking (Ruby & Decety, 2003; Samson et al., 2005). That is, inferring another person's perspective requires successful inhibition of the own perspective. This idea was first proposed by Vorauer and Ross (1999) who suggested that occasional misapprehensions of other's mental state may be caused by an automatic tendency to assume one's own mental state as a correct model for others (Gilovich et al., 2000; Markus et al., 1985) and that this automatic tendency is induced by a failure to suppress one's own perspective.This automatic tendency may be induced by a failure to suppress one's own perspective, which has been linked to limited inhibitory control (Carlson et al., 2004). This was demonstrated in young children (Sommerville & Woodward, 2005; Wellman et al., 2001), adults suffering brain damage (Apperly et al., 2004; Gregory et al., 2002; Rowe et al., 2001; Stone et al., 1998) and psychiatric patients [e.g. autism and schizophrenia (Baron-Cohen et al., 1985; Corcoran et al., 1995; Langdon et al., 2002; Leslie & Thaiss, 1992)]. A two-component ToM model was proposed comprising (1) a perspective taking component and (2) a self-perspective inhibition component (Ruby & Decety, 2003; Samson et al., 2005). That is, being able to infer another person's perspective requires successful inhibition of the own perspective. In **chapter 2** of this thesis, the hypothesis that each component relies on a different neural substrate was discussed. Moreover, we discussed the hypothesis that such complex social processes may be based upon 'simple' cognitive processes such as simple response inhibition.

A large body of research has demonstrated that ToM is often impaired in patients with schizophrenia [see Bora et al. (2009c) for a meta-analysis], and also in their family members (Krabbendam et al., 2001), leading to the proposition that ToM may be a trait characteristic of the disorder. Neuroimaging studies have shown abnormal activation patterns in medial and lateral prefrontal regions as well as inferior parietal regions in patients with schizophrenia while performing ToM tasks (Brunet-Gouet & Decety, 2006). Abnormalities in ToM processing have not just been described schizophrenia, but also in subjects with an enhanced risk for schizophrenia like relatives of patients (Marjoram et al., 2006) and healthy subjects who are prone to psychosis (psychosis proneness; PP) (Barragan et al., 2010; Langdon & Coltheart, 2004; Pickup, 2006; Versmissen et al., 2008). PP, also called schizotypy, refers to a broad range of sub-clinical experiences and personality characteristics that are related to psychosis in the general population (Claridge et al., 1996; Meyer & Hautzinger, 2002). PP subjects are thought to have biological and/or cognitive predispositions for the development of psychosis later in life (Lenzenweger, 2006; Suhr, 1997). Longitudinal studies have demonstrated that approximately 10% of the PP subjects will develop a schizophrenia spectrum disorder in the future (Chapman et al., 1994; van Os et al., 2009). This subclinical group of subjects is especially interesting because it allows us to study the effects of psychotic like experiences without confounding factors such as medication.

As described above, impairments in ToM have been attributed to a failure in the inhibition of the own perspective. In **chapter 3** of this thesis self-perspective inhibition and other-perspective taking was tested in high and low PP subjects. We expected to find behavioral differences in self-perspective inhibition as well as a different brain activation pattern between high and low PP subjects. In addition, we expected to find a relationship between self-perspective inhibition performance and performance on simple response inhibition. If indeed impairments in such inhibitory processes underly difficulties in ToM, this may provide clues for improvement of such skills through psychotherapy or other forms of cognitive training.

Emotional processing and alexithymia

Understanding and interpreting the feelings and intentions of others may be related to the ability to understand one's own feelings (Lane & Schwartz, 1987; Moriguchi et al., 2006). Identifying one's emotions, subsequently analyzing these emotions and putting these emotions into words (or verbalizing them) is a skill in itself. If one or more of these processes is impaired this is called alexithymia, literally 'no words for feelings' (Sifneos, 1973). Alexithymia is a multidimensional construct that includes difficulties identifying one's feelings, describing feelings to other people as well as appraising bodily sensations of emotional arousal, constricted imaginary processes and an externally oriented cognitive style with a relative lack of introspection (Bermond et al., 2006; Sifneos, 1973; Taylor et al., 1997). Alexithymia has been linked to emotion regulation difficulties (Connelly & Denney, 2007; Taylor et al., 1997). The

concept of emotion regulation refers to a diverse set of processes by which "individuals influence which emotions they have, when they have them, and how they experience and express these emotions" [cf. Gross (1999) p. 557]. Two well-studied regulation strategies are emotional suppression or reappraisal of emotions to decrease (or increase) emotional response tendencies or affective states (Frijda, 1988; Gross, 1998).

Suppression is defined as the concious inhibition of emotion-expressive behavior (facial affect, verbal expression and gestures) during a state of emotional arousal (e.g. keeping a poker face when playing cards) (Gross & Levenson, 1993). Reappraisal is the reinterpretation of emotionally valenced stimuli in unemotional terms (e.g. reinterpreting a disturbing remark so it is less disturbing) (Speisman, 1964). The use of suppression takes place when the emotion has already been generated and results in little or no change in emotional experience. Instead reappraisal actually changes the emotional feeling (Gross, 1998). After evaluating emotional cues and the triggering of accompanying responses, emotion regulation can be seen as the finetuning of emotional responses (Gross, 1998). To what extent people use both emotion regulation strategies in daily life can be measured with a self-report questionnaire [Emotion Regulation Questionnaire; ERQ (Gross & John, 2003)].

The relationship between alexithymia and impairments in emotion regulation has not been investigated in schizophrenia patients, even though higher alexithymia scores (Cedro et al., 2001; Stanghellini & Ricca, 1995; van 't Wout et al., 2007) and emotion processing impairments have been found in this patient group (Aleman & Kahn, 2005; Edwards et al., 2001; Kohler et al., 2003). In **chapter 4** the hypothesis that schizophrenia patients would score higher on alexithymia and would make more use of the suppression strategy of emotion regulation was tested.

Emotion regulation and the brain

Besides measuring the self-reported use of emotion regulation in daily life through questionnaires, underlying neural mechanisms of both reappraisal and suppression strategies have been investigated through functional Magnetic Resonance Imaging (fMRI) (Goldin et al., 2008; Ochsner et al., 2002). Reappraisal demonstrated an increase of activation in dorsolateral and ventrolateral prefrontal cortex (d & vLPFC) and dorsal anterior cingulate cortex (dACC) as well as a decrease in the limbic areas, such as insula and amygdala at an early stage of the regulation process (Goldin et al., 2008; Ochsner et al., 2002). Instead, suppression occurred at a later stage in the regulation process and produced less activation in medial and inferior frontal regions and increased activation in the insula and amygdala (Goldin et al., 2008). Goldin et al. (2008) suggested that the PFC is involved in the down-regulation of the amygdala during reappraisal, whereas the lack of PFC activation in suppression resulted in maintainance or even increase of activation in lymbic areas, such as the amygdala and insula. To date, the neural mechanisms underlying these emotion regulation

strategies have only been described in healthy subjects. However, there is behavioral evidence that schizophrenia patients differ from healthy control subjects with regard to the use of both emotion regulation strategies. That is schizophrenia patients make more use of the suppression strategy than healthy controls, while they tend to use the reappraisal less often (chapter 4 of this thesis; Livingstone et al., 2009). These findings may explain the blunted affect (i.e. diminished expression of emotion) in schizophrenia patients when experiencing emotions, which has so often been described (Kring & Neale, 1996; Morris et al., 2009).

Not only in schizophrenia patients, but also in their non-affected relatives impairments on a range of cognitive tasks as well as abnormalities in emotional processing have been demonstrated (Phillips & Seidman, 2008) although less severe than in patients (Keshavan et al., 2010; Sitskoorn et al., 2004). In the last decade there has been a remarkable increase in studies of first-degree relatives of patients with schizophrenia. It is estimated that first-degree relatives of patients with schizophrenia share approximately 50% of their genes with their ill relative (Phillips & Seidman, 2008) and have a ten-fold increased risk for developing schizophrenia or other psychiatric disorders (MacDonald III et al., 2009). Unaffected relatives are free from neurophysiologic and psychological changes that may occur as an effect of the acute psychotic state. In addition, they are free from the neurophysiological and psychological changes induced by antipsychotic medication (MacDonald III et al., 2009). Thus, these relatives form an excellent focus-point in the search for markers of vulnerability and for unraveling the etiology of schizophrenia (Kéri & Janka, 2004; MacDonald III et al., 2009). In **chapter 5** the neural correlates of emotion regulation strategies reappraisal and suppression were discussed for schizophrenia patients as well as first degree relatives. Differences between groups in activation of prefrontal regions were expected. Since reappraisal requires more prefrontal activation, these differences were expected to arise mainly for this regulation strategy. More specifically, we expected that patients would be impaired on the reappraisal strategy and would demonstrate less activation in prefrontal regions compared to healthy control subjects. However, with regard to the relatives, expectiations are more difficult to express. If emotion regulation impairments follow a linear process, one would expect that relatives would show intermediate activation compared to healthy controls and patients. However, some studies indicate that relatives show increased activation instead [see MacDonald III (2009) for a review]. This is usually explained as a compensatory mechanism, necessary to perform well on a certain task. Thus both hypotheses seem valid. We tested the hypothesis that relatives would differ from both healthy controls as well as schizophrenia patients, but did not express an explicit expectation with regard to the direction of this effect.

Self-reflective processing

Not only ToM and emotion regulation are important skills for the interaction with the social world. Having an accurate representation of one's traits, abilities and

attitudes is essential in the evaluation of one's own behavior and comparing it with the behavior of other human beings. This evaluation process is referred to as self-reflective processing. To investigate which brain areas are involved in such self-reflective processing, the most commonly used paradigm uses trait adjectives or sentences that are presented to a subject. The subject is subsequently asked whether the trait or sentence applies to him/her. Results have consistently pointed to a role of medial brain areas encompassing the posterior cingulate cortex (PCC), anterior cingulate cortex (ACC) and the dorsomedial as well as the ventromedial prefrontal cortex (d & vMPFC), together also called the cortical midline structures (CMS), in these self-reflection processes. It has been shown that patients who have suffered damage to the CMS have difficulties in properly evaluating the social and cognitive difficulties they encounter and often overestimate their capacities as well as their performance particularly on cognitively demanding operations (Schmitz et al., 2006). Despite the available evidence, this has not allayed misgivings with regard to the concept of self-reflective processing (Gillihan & Farah, 2005). More specifically, whether the processing of self-reflective information is substantially different from the processing of information concerning other people. To concatenate the available evidence with regard to the neural basis of self-reflective processing, other-reflective processing and the difference between both processes, a meta-analysis of neuroimaging findings is presented in **chapter 6** in this thesis. We included studies administering self-reflection paradigms in which trait characteristics (words or sentences) were presented and which reported significant peak activations for comparisons between self-reflective processing and baseline, or self-reflective processing and other-processing. Based upon the results of the meta-analysis, we proposed a model for self- and other-reflective processing. Moreover, in chapter 6 the implications of impaired self-reflective processing will be discussed. Dimaggio et al. (2008) argued that to be able to recognize emotions in others, one needs to be able to recognize one's own emotions. That is, to be able to put yourself in another person's shoes, you use your own perspective as a basis for the interpretation (Carruthers, 2009). In addition, recognizing one's own emotions is needed before subsequent regulation of that emotion can be initiated. These suggestions put the process of self-reflection at the basis of processes such as emotion regulation and ToM, while the ability to evaluate yourself also requires ToM. When self-processing is hampered this can lead to major problems in the social domain, particularly in the domain of behavior modification in a social situation as well as in the recognition of social cues (Atkinson & Robinson, 1961). This typically is one of the major problems encountered by schizophrenia patients and may not just lead to problems in the interaction with other people, but may also bring about problems in the integration of such social cues into the own self-image.

Patients, who experience difficulties in reflecting upon themselves, will most likely also have difficulty reflecting upon themselves in the light of their illness, symptoms and use of medication. The awareness of illness, symptoms and necessity of treatment is also referred to as insight. In chapter 6, the consequences of hampered

self-reflective processing in patients with schizophrenia and the possible consequences for insight were discussed.

Illness insight

Lack of illness insight is a common feature in patients with a psychotic disorder and refers to the lack of awareness that one suffers from a mental disorder as well as lack of awareness regarding the concequences of the disorder and the need to treat these symptoms. The concept of illness insight has been fragmented into three components by David (1990): (1) the awareness that one suffers from a psychiatric disorder, (2) the attribution of symptoms to the disorder and (3) recognizing the need for treatment. These three dimensions have been confirmed by factor analyses on questionnaires and interviews that assess these differential aspects of insight (David, 2004).

Impaired insight has been mentioned as one of the most frequently reported symptoms of schizophrenia. Nevertheless, insight is not decribed in DSM nor in ICD classifications, despite the emphasis of patients' societies on the consequences of impaired insight for the patient. Lack of insight has been associated with poorer global functioning (Dickerson et al., 1997; Pyne et al., 2001; Stefanopoulou et al., 2009a), severity of psychopathology (Mintz et al., 2003), increased relapse and hospitalizations, poorer long term prognosis (Schwartz, 1998), and reduced treatment compliance (Kemp & David, 1996; Yen et al., 2005). Obviously, impaired insight often leads to frustations in family members and clinicians. The past decade has seen a surge of interest not only at the underlying cognitive mechanisms of impaired insight, but also in treatment programs aimed at the improvement of insight (Lysaker et al., 2010a).

Prevalence of impaired insight is difficult to estimate, especially since the patients with the most impaired insight often do not seek professional assistance. Especially this patient group is treated only after a judicial mandate. Prevalence numbers of impaired insight vary between 50%-85% of schizophrenia patients (Amador et al., 1994; Carpenter et al., 1973; Dam, 2006). Importantly, impaired insight is not just problematic in patients with schizophrenia, but also in patients with other psychiatric disorders, such as bipolar disorder. In bipolar disorder approximately 63 % of the patients have impaired insight comparable to that of schizophrenia patients (Dell'Osso et al., 2002; Ghaemi & Rosenquist, 2004; Keck, Jr. et al., 1997; Pini et al., 2001; Varga et al., 2006). This mainly applies to patients in the manic phase of the illness and to a lesser extent for patients in a euthymic or more stable phase of the disorder (Dell'Osso et al., 2002; Ghaemi & Rosenquist, 2004; Varga et al., 2006).

Several instruments for measuring insight are available. One of the most widely used interviews administered in schizophrenia patients is the Positive And Negative Syndrome Scale [PANSS; (Kay et al., 1987)]. This interview contains one item (G12) that assesses insight. Even though this item does not discriminate

between different dimensions of insight, it still provides information with regard to the insight of the patient. More extensive semi-structured interviews measuring of insight are the Scale to Assess Unawareness of Mental Illness [SUMD; (Amador et al., 1993)], the Schedule to Assess components of Insight -Extended [SAI-E; (Kemp & Davis, 1997)], the Insight and Treatment Attitude Questionnaire [ITAQ; (McEvoy et al., 1989)]. Finally, self-report questionnaires have been developed to measure insight, the Birchwood Insight Scale [BIS; (Birchwood et al., 1994)] and the Beck Cognitive Insight Scale [BCIS; (Beck et al., 2004)]. These and other measures of insight are discussed in Amador en Kronengold (2004).

Intuitively one would expect that symptomatology would be associated with illness insight, however, this relationship does not appear to be that straightforward (McEvoy et al., 1989; Mintz et al., 2003). Mintz and colleagues (2003) reported a significant correlation ($r = 0.25$) between positive symptoms and insight, which was the same as the relationship between negative symptoms and insight. Even though this effect was statistically significant, the effect is rather small leaving room for other explanations for impaired insight.

Three approaches to investigate the concept of insight can be distinguished: (1) the clinical approach, (2) the psychological defense approach and (3) the neuropsychological approach. In the clinical approach insight is considered as a primary symptom of the disorder (Cuesta & Peralta, 1994). That implies that, like other primary symptoms such as hallucinations and delusions, impaired insight arises directly from the psychosis. As a secondary symptom, impaired insight would be seen as a behavioral response to the occurrence of primary symptoms. This clinical approach assumes that there is no relationship between symptomatology and hence can be seen as a primary symptom. However, in the literature this interpretation is disputed (Cooke et al., 2005). Despite the finding that impaired insight is not independent from symptoms (Mintz et al., 2003), independency from current symptoms does not justify the complete separation of symptoms and impaired insight. Insight also refers to the awareness of current and past symptoms, which makes it nearly impossible to consider both concepts independently. Moreover, the clinical approach focuses upon this relationship between symptomatology and insight and does not go into the underlying cognitive or neural processes of insight (Cooke et al., 2005).

The defense approach assumes that denial is used as a defense system and hence can cause impaired insight. Even though this approach is intuitively appealing, not much scientific evidence is available to support this hypothesis. Subotnik et al. (2005) showed that patients with impaired insight have a higher score on measures of psychological defensiveness. These patients scored higher on guardedness, psychological suppression, attempting to present oneself in a socially desirable light, and social acquiescence.

The underlying reasoning is that accepting the label of a psychiatric disorder has a negative effect on the self-image of an individual, which is reflected in the relationship between insight and depression [$r=0.18$; (Lincoln et al., 2007)]. This

implies that the better the insight, the more depressive symptoms or vice versa. The direction of this association remains as yet unclear, which complicates the interpretation of the relationship. A mediating factor between insight and depression has been proposed for internalized stigma (Tranulis et al., 2008a). Accepting a diagnosis can be threatening for the self-image as well as for other peoples' judgment of yourself and may induce depressive symptoms. Indeed, patients who have internalized the stigma of the society and who have good insight, report more depressive symptoms (Lysaker et al., 2005a; Lysaker et al., 2008a; Lysaker et al., 2008b), while patients with good insight and who did not internalize societies stigma report less depressive symptoms (Cooke et al., 2007; Staring et al., 2009). Even though this approach is intuitively appealing, it still allows for two diverging interpretations: (1) the patient has insight, but refuses to accept this situation and thus uses denial as a coping strategy and (2) the denial process occurs subconsciously, resulting in a 'true' lack of insight in the patient. The denial approach does not distinguish between both interpretations.

The third, most influential approach is the neuropsychological approach, which draws a parallel between insight in psychiatric disorder and insight in neurological disorders or *anosognosia*. Anosognosia was first described by Babinski (1914). Patients with for example paralysis of limbs can deny that they cannot use this limb. Anosognosia can be limited to one domain. That is, patients can deny for example paralysis of the hand, but can acknowledge visual handicaps (Marcel et al., 2004). Even though anosognosia often is more specific and mostly concerns only one modality, the parallel between insight in neurological and psychiatric disorders suggests that similarly impaired cognitive processes may cause impaired insight in psychiatric disorders (Amador & Seckinger, 1997; McGlynn & Schacter, 1997). Thus, in the neuropsychological approach of impaired insight in psychiatric disorders, cognitive processes resulting from frontal lobe disfunctions are proposed to underly impaired insight (Cooke et al., 2005; Larøi et al., 2004; Lysaker & Bell, 1994; Young et al., 1993).

Insight and cognitive functioning

A meta-analysis by Aleman et al. (2006) reported a significant relationship between cognitive functioning and insight (r=0.17), of which set-shifting or cognitive flexibility and error monitoring were most influential. Cognitive flexibility refers to the capacity to switch between cognitive sets, which is often tested with the Wisconsin Card Sorting Task (WCST). This task measures the ability to discover changes in rules and subsequently adapt ones behavior to this changed rule. Mental flexibility is necessary to put the own behavior into perspective. Aleman et al. (2006) demonstrated that schizophrenia patients with impaired insight are significantly more impaired on this task than patients with better insight. However, the association reported in Aleman et al. (2006) can only explain a very small part of the variance (3%), indicating that mental flexibility cannot be the whole story. Koren et

al. (2004) have administered an adapted version of the WCST in patients with good and impaired insight and also asked patients to evaluate their own performance. They demonstrated a strong relationship between insight and the ability to evaluate the own performance, also called meta-cognition. If this meta-cognitive evaluation is applied to the evaluation of ones own traits and capacities, this may be called self-reflective processing. Lysaker et al. (2005b) have demonstrated that schizophrenia patients with good insight were better at evaluating their own thoughts. Importantly, they were not just better at the evaluation of the own thoughts, but also at the evaluation of the thoughts and actions of other people, theory of mind (ToM). Results show that insight will be the best in patients who are able to empathize with others (Bora et al., 2007; Langdon & Ward, 2009; Pijnenborg et al., 2010). It was suggested previously that insight could improve through perspective taking (Gambini et al., 2004). Since perspective-taking is thought to be build upon the ability to take the own perspective by using the own perspective as a model to infer the mental state of others, the common denominator in both processes may be self-reflective processing. This makes self-reflection an interesting candidate as a core process that may be hampered in impaired insight.

Insight, social cognitive and emotional processing

The above reasoning illustrates that besides cognition and symptoms of the illness, social cognitive and emotional processes may well be important in explaining impaired insight. To investigate the additional explanatory power of social factors, we investigated neurocognitive measures, symptoms as well as social emotional factors in patients with schizophrenia as well as in patients with bipolar disorder. Most of the studies that have investigated insight, either looked at social cognition and insight or neurocognition and insight. The additional explaining power of both concepts with regard to insight in addition to the symptomatology has not been investigated before. In **chapter 7**, the relationship between insight, neurocognitive factors, symptoms and social factors in schizophrenia was described. It was expected that not only neurocognitive factors and symptomatology would be related to insight, but that social cognitive factors would be additionally related to insight. Thus, this study investigated the combined explanatory power of all three concepts for insight.

In **chapter 8** we investigated a similar relationship between neurocognitive factors, social factors and symptoms in patients with bipolar disorder. Some studies demonstrated a clear association between neurocognitive performance and insight (Adida et al., 2008; Dias et al., 2008; Varga et al., 2006; Varga et al., 2007), while others showed no relationship at all on similar measures (Arduini et al., 2003). The association between social factors and insight in bipolar disorder has not been investigated to date. This is remarkable in view of impairments in social and emotional processing that are present in bipolar patients, such as the perception of emotional stimuli and emotional faces (Bozikas et al., 2006; Kalmar et al., 2009;

Phillips et al., 2008; Summers et al., 2006), emotion regulation (Wessa et al., 2007) and emotional memory (Kauer-Sant'Anna et al., 2008). In addition, we investigated the mediating influence of lifetime psychotic features in the bipolar patients, since insight is sometimes considered as a core feature in psychosis (Kraepelin, 1919) and patients with lifetime psychotic features demonstrate worse cognitive impairment than patients without lifetime psychotic features (Bora et al., 2009b; Bora et al., 2010). Similar to our expectations with regard to insight in schizophrenia, we expected to find the most explanatory power in a model that encompasses neurocognition, symptomatology as well as social cognitive factors.

Finally, in **chapter 9,** we discussed and combined the findings of the presented studies. Furthermore, the clinical implications of the findings and directions for future research were explored.

In sum, in this thesis mental processes that we all use in daily social interactions, which may be compromised in patients with schizophrenia and bipolar disorder are presented. More specifically, such abnormalities may mediate the extent to which a patient is able or willing to consider the implications of the disorder from which he/she is suffering, the symptoms that are defining the disorder and the treatment that may be necessary to overcome many difficulties and consequences that come with the disorder. The topics that are addressed in this thesis are still subject of our current research interest. Therefore, in the time to come, we hope to be able to present more results with regard to the proposed relationship between insight in schizophrenia and bipolar disorder and the importance of social cognitive processing in this relationship.